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Review

First-in-class drug oroxylin A tablets for treating hepatic and gastrointestinal disorders: from preclinical development to clinical research

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ABSTRACT

Oroxylin A (OA) is a natural flavonoid primarily derived from the plants *Oroxylum indicum* and *Scutellaria baicalensis*. Currently, OA is obtainable through chemical synthesis and exhibits polypharmacological properties, including anti-cancer, anti-inflammatory, anti-microbial, and multi-organ protective effects. The first-in-class drug OA tablets are presently undergoing phase Ib/IIa clinical trials for hepatocellular carcinoma (HCC) treatment. Substantial evidence suggests that OA demonstrates therapeutic potential against various hepatic and gastrointestinal (GI) disorders, including HCC, hepatic fibrosis, fatty liver disease, hepatitis, liver injury, colitis, and colorectal cancer (CRC). OA exerts its therapeutic effects primarily by modulating several crucial signaling pathways, including those associated with apoptosis, oxidative stress, inflammation, glucolipid metabolism, and fibrosis activation. The oral pharmacokinetics of OA is characterized by phase II metabolism, hydrolysis, and enterohepatic recycling. This review provides a comprehensive overview of the critical stages involved in the development of OA tablets, presenting a holistic perspective on the progression of this first-in-class drug from preclinical to clinical phases. It encompasses the synthesis of active pharmaceutical ingredients, pharmacokinetics, pharmacological efficacy, toxicology, drug delivery, and recent advancements in clinical trials. Importantly, this review examines the potential mechanisms by which OA may influence the gut-liver axis, hypothesizing that these interactions may confer health benefits associated with OA that transcend the limitations posed by its poor bioavailability.

1. Introduction

The integration of natural ingredients in drug discovery has recently emerged as a promising approach, attributed to their unique chemical structures and potential biotherapeutic properties [1-5]. Numerous natural compounds have demonstrated therapeutic efficacy in addressing disorders of the gastrointestinal (GI) and hepatic systems [6-8]. Notable examples include miltirone, apigenin, silymarin, cardamonin, baicalin, and glycyrrhizin, which have been utilized in the management of hepatic fibrosis, viral hepatitis, fatty liver disease, and cirrhosis [7-11]. Additionally, emerging research indicates that the pharmacological activities of various natural products are influenced by gut microbiota, which in turn is modulated by these natural products [12-15]. Oroxylin A (OA), a naturally occurring flavonoid, is predominantly found in plants such as *Oroxylum indicum*, *Scutellaria baicalensis*, *Scutellaria lateriflora*, which is employed in both Ayurveda and traditional Chinese medicine (TCM) [16, 17]. Extensive *in vitro* and *in vivo* investigations have elucidated a diverse array of pharmacological properties of OA, encompassing anti-cancer, anti-inflammatory, antioxidant, cardioprotective, hepatoprotective, and neuroprotective effects [17-21]. This polypharmacology can be attributed to OA's capacity to interact with multiple pathways and bind to various signaling molecules [22-28]. Additionally, OA demonstrates anti-obesity [29], anti-dyslipidemic [30], and anti-viral [31], which contribute to the enhancement of hepatic function post-injury, the amelioration of alcohol-related liver diseases, and the induction of apoptosis in proliferating hepatocytes [32, 33].

From 1998 to October 2024, a total of 469 publications concerning OA were indexed in the Web of Science Core Collection. An analysis of the geographical distribution of this research indicates that OA studies are conducted across 25 countries and regions globally (Fig. S1). China leads in the number of published studies, contributing 333 papers, followed by South Korea with 48, India with 25, the United States with 11, and Japan with 10. This distribution highlights a significant concentration of research activity in East Asia, which can be attributed to the historical foundations of OA in traditional East Asian medicinal systems, particularly TCM. A comprehensive keyword frequency analysis was conducted to identify the predominant themes and emerging trends within the OA research literature. Besides "OA", the most frequently occurring keywords include "*Scutellaria baicalensis*" "baicalein" and "flavonoids", suggesting a notable focus on this traditional medicinal herb and its associated flavonoids. "Pharmacokinetics" also appears as a prominent keyword.

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Concerning biological mechanisms and diseases, the most commonly referenced terms encompass “apoptosis” “inflammation” “oxidative stress” “autophagy” “angiogenesis” and “glycolysis” indicating that OA is extensively studied for its ability to regulate key cellular processes involved in various diseases. The terms “hepatocellular carcinoma (HCC)” “liver fibrosis” and “colorectal cancer (CRC)” emphasize OA’s therapeutic focus on hepatic and GI disorders. Furthermore, the inclusion of emerging diseases such as “COVID-19” demonstrates the adaptability of OA research in addressing current global health challenges.

In August 2020, the National Medical Products Administration (NMPA) granted clinical approval for OA tablets developed by China Pharmaceutical University as a Class 1 new drug (No. CXHL2000302), permitting clinical research with HCC as the initial indication. Additionally, approval was obtained for a multi-tumor indication (No. CXHL2300375), encompassing solid tumors such as colorectal and gastric cancers, as well as hematological malignancies. This review provides a comprehensive overview of the critical phases in OA development, covering both preclinical and clinical stages relevant to the treatment of GI and liver-related disorders. It establishes a theoretical foundation for the clinical advancement of OA and the exploration of its novel applications, while also offering valuable insights for the development of new drug candidates derived from natural products.

2. Sources of OA

O-Methylated flavone, known as OA, was initially identified and named by Shahden et al. who isolated the compound from the root bark of *Oroxylum indicum* in 1936 [34]. It has been extensively studied as a principal constituent components of *Scutellariae baicalensis* and *Scutellaria lateriflora* [35]. In recent years, researchers have also identified OA in various other plant species, including *Stachys geobombycis* [36], *Capparis spinosa* [37], *Ardisia crispa* [38], *Eucommia ulmoides* [39], *Aster himalaicus* [40], and *Anchietea pyrifolia* [41] (Fig. 1).

Oroxylum indicum, a medicinal herb from the Bignoniaceae family, is widely distributed across Asian regions. For centuries, it has been utilized in traditional medicine for the prevention and treatment of various ailments, including arthritis, rheumatism, gastric ulcers, tumors, respiratory disorders, diabetes, diarrhea, and dysentery [42]. The therapeutic properties of this herb are largely attributed to its secondary metabolites, with flavonoids being the predominant constituent [43-45].

Scutellariae baicalensis is a prominent medicinal herb utilized in TCM, native to several Asian countries, including China, Japan, and Korea [46]. *Scutellaria lateriflora*, commonly known as blue skullcap, mad dog skullcap, and side-flowering skullcap, is indigenous to wetland areas from Quebec and Newfoundland. The dried root of these plants, referred to as Scutellariae Radix or Huangqin, contains various flavonoids and flavone glycosides [47]. Recent clinical research has demonstrated the efficacy of Scutellariae Radix in treating diseases such as hepatitis, hypertension, acute respiratory infections, and acute gastroenteritis [48-50]. In addition to OA, other significant flavonoids present in Scutellariae Radix, such as baicalin, baicalein, and wogonin exhibit potential therapeutic effects in managing GI and liver diseases [51-56].

Capparis spinosa, commonly known as caper, is a perennial species belonging to the Capparaceae family and is predominantly distributed in tropical regions. Multiple studies have demonstrated the numerous benefits of capers, including anti-oxidant, anti-tumor, hypoglycemic, anti-bacterial, anti-ulcer, anti-arthritic, and immunomodulatory activities.

Ardisia crispa, belonging to the Myrsinaceae family, is distributed in the southern provinces of the Yangtze River Basin in China, with its root used medicinally. Modern research indicates that *Ardisia crispa* is rich in triterpene glycosides, flavonoids, isocoumarins, and other chemical constituents. It exhibits heat-clearing and pharyngeal effects, as well as tendon activation properties. It is used to treat sore throat, tonsillitis, nephritis, edema, and other diseases, earning it the moniker “laryngeal medicine” [57].

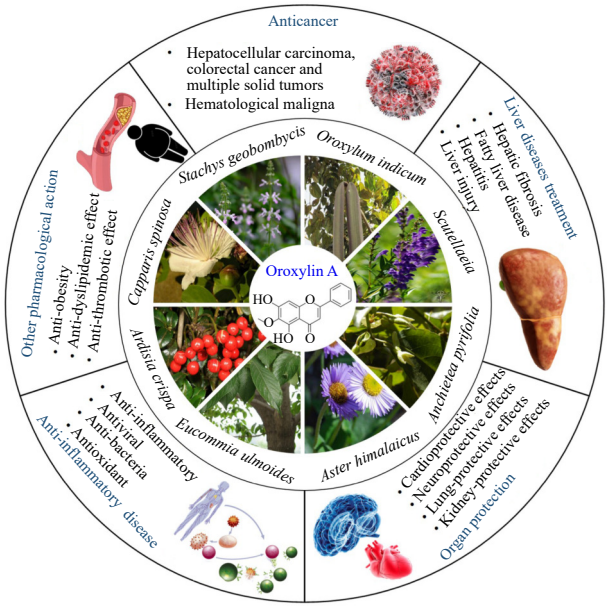

Fig. 1 Overview of the main sources and polypharmacologic actions of OA.

Eucommia ulmoides, a plant belonging to the Eucommiaceae family, was first recorded in the *Shen Nong Ben Cao Jing* and has been used for over 2000 years, surviving only in China. The bark, leaves, seeds, and even male flowers are commonly utilized as medical remedies and have demonstrated remarkable therapeutic effects on hypertension, hyperglycemia, diabetes, obesity, osteoporosis, Parkinson’s disease, Alzheimer’s disease, and sexual dysfunction [58].

Stachys geobombycis predominantly thrives in areas such as Hunan and Fujian provinces in China, and possesses properties that facilitate heat and toxin elimination, support renal function, and provide other benefits. *Anchietea pyrifolia* is a woody liana (Violaceae) from Brazil, and *Aster himalaicus* is a broadleaf deciduous perennial with green foliage. Currently, there is a limited number of publications regarding the pharmacological investigations of the monomeric constituents of these three plant species. Existing studies indicate that OA is among the components exhibiting growth inhibitory effects on tumor cells.

3. Preparation and synthesis of OA

A substantial portion of approved molecular entity drugs are either directly derived from natural products or modifications thereof [59]. OA, characterized as a yellow, needle-like crystal with the molecular formula $C_{16}H_{12}O_5$, is chemically designated as 5,7-dihydroxy-6-methoxyflavone. The lipophilicity parameter log *P* value of OA is 2.73, and its solubility is measured at 66.60 $mg{\cdot}L^{-1}$ [60]. The conventional method for isolating OA from *Oroxylum indicum* and *Scutellaria* employs high-speed counter-current chromatography (HSCCC) [61, 62]. Previous investigations have indicated that the compound referred to as “OA” isolated from *Oroxylum indicum* was actually a mixture of three distinct substances [63]. However, researchers were unable to achieve a complete separation of these components. Ultimately, Row et al. successfully purified OA through the fractional crystallization of acetates in ethanol, thereby confirming that OA is indeed the 6-*O*-methylated derivative of baicalein [63]. Nevertheless, the limited water solubility of OA, combined with the complex separation

and extraction methodologies and the resulting low yield, presents significant obstacles to the industrial application of this compound. Researchers have engaged in collaborative efforts to address the technical challenges associated with the chemical synthesis of OA.

In the initial phases of the research, investigators utilized wogonin as the precursor compound, which was subsequently subjected to partial benzylation to yield 7-benzyl wogonin. Following this, isomerization reactions were employed to convert 7-benzyl wogonin into 7-benzyl baicalein, and then the deprotection of the benzyl group, resulting in the formation of OA [64]. This synthetic approach involves several reaction steps, incurs significant costs, and is primarily applicable for research purposes, thereby rendering it impractical for large-scale production. Currently, baicalin and baicalein are widely available and commonly utilized as the primary raw materials for the synthesis of OA. Previous research has frequently conflated OA with its regioisomer, negletein (5,6-dihydroxy-7-methoxyflavone), leading to erroneous synthesis. Hemantha et al. developed a new method for OA preparation that avoids the complications associated with negletein and reduces the number of protection/deprotection steps, achieving a yield of 70%–75% (Fig. 2i). This method entails the acid-catalyzed esterification of the sugar moiety's carboxy group with methanol, selective base-catalyzed methylation of the C-6 phenolic group, and acid-mediated hydrolysis to cleave the glucuronide from the aglycone [65]. Furthermore, Li et al. established a widely recognized method for the large-scale production of OA from baicalein (Fig. 2ii). This method involves the reaction of baicalin with benzyl bromide and benzyl chloride, followed by methylation with dimethyl sulfate and final debenzylation using palladium-carbon catalytic hydrogenation [66]. An alternative approach for the preparation of OA from baicalin, as reported by Hemantha et al., attains a total yield of 62% while conforming to the principles of green chemistry (Fig. 2iii). This method involves acidic hydrolysis to produce baicalein, acetylation to form baicalein 6,7-diacetate, methoxymethyl (MOM) protection at the C-7 position, selective methylation at the C-6 position, and final deprotection of the MOM group [67]. Additionally, research has indicated the biosynthesis of OA utilizing *Escherichia coli*; however, this investigation is also hindered by its inability to accurately differentiate between negletein and OA [68]. In the study, a glycosyltransferase was initially utilized to regioselectively transfer glucuronic acid from uridine 5'-diphospho (UDP)-glucuronic acid to the 7-hydroxy group of baicalein, resulting in the synthesis of baicalin. Following this, two *O*-methyltransferases (OMTs), specifically ROMT-15 and POMT-9, were employed to facilitate the synthesis of negletein and OA, respectively.

4. Preclinical oral pharmacokinetics (PK) and toxicity of OA

The administration of traditional herbal medicines typically occurs *via* oral routes, with the liver and GI tract serving as the primary metabolic disposal sites. The metabolism within the intestinal tract significantly influences the *in vivo* behavior and pharmacological activity of natural compounds, particularly flavonoids [69]. Upon absorption, flavonoids undergo glucuronidation, a reaction facilitated by hepatic metabolic enzymes, which enhances their polarity. This results in their excretion into the intestinal lumen *via* bile, where intestinal flora subsequently degrade them into glycosides. These glycosides are then reabsorbed into the systemic circulation, resulting in enterohepatic recycling. The pharmacokinetic characteristics of OA in the GI system exhibit similarities to those of its isomer wogonin and its homolog baicalin, encompassing processes such as hydrolysis,

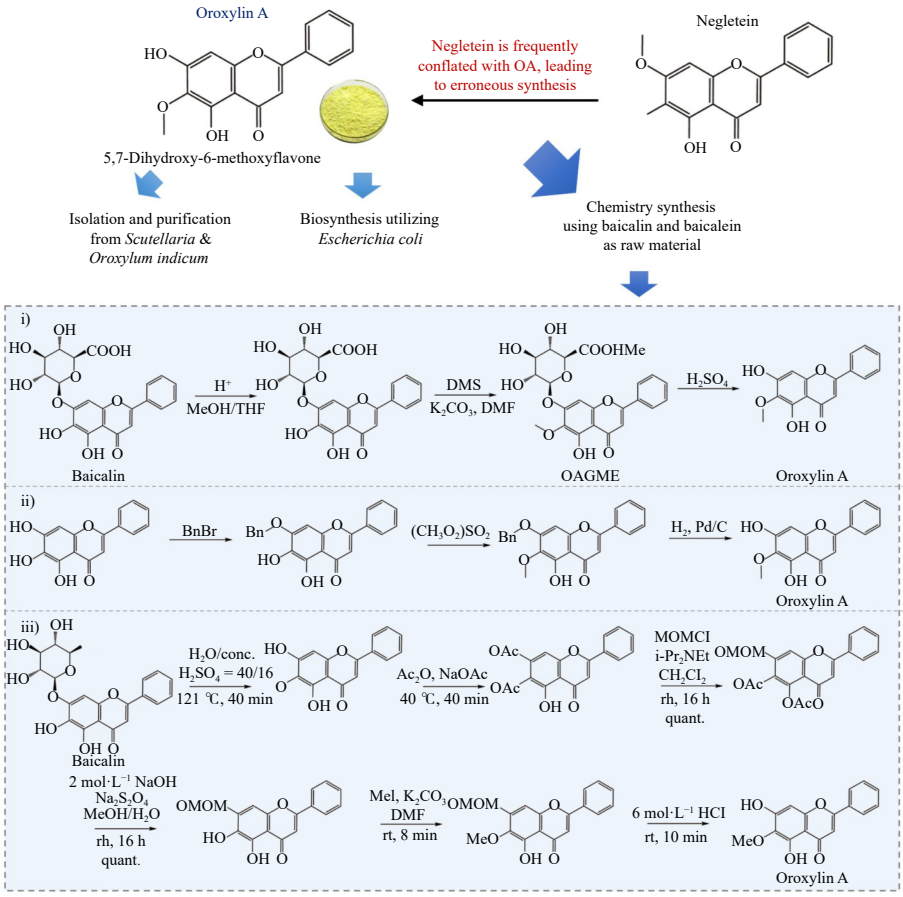

Fig. 2 Preparation and synthesis of OA.

enterohepatic recycling, and carrier-mediated transport [70-73]. Oral OA undergoes primary metabolism through phase II reaction in animal models, with the principal active metabolites identified as OA 7-*O*-glucuronide (OG) and OA sodium sulfonate (OS) [74, 75]. Notably, OG emerges as the predominant metabolite, regardless of whether OA is administered *via* intravenous (in rat, dog) or oral routes (in mice, rats, dog and healthy human). The glucuronidation of OA is facilitated by UDP-glucuronosyltransferases (UGTs) in the liver and intestinal microsomes [76]. Furthermore, OA possesses the ability to traverse the blood-brain barrier, suggesting its potential neuroprotective effects against various neurodegenerative disorders [77, 78]. A cellular pharmacokinetic investigation revealed that both OA and OG were predominantly distributed into nuclei of tumor cells post-uptake. Additionally, OG was found to distribute into mitochondria, indicating a possible alternative target for its action [79]. The overview of pharmacokinetics OA is shown in Table S1.

A single intravenous administration of OA is rapidly eliminated from the body. In contrast, the administration of OA presents a more complex scenario, as a number of intestinal processes, including permeation, efflux, and metabolism, exert a substantial influence on the oral bioavailability of flavonoids [80, 81]. In a study involving SD rats, the elimination half-life ($T_{1/2}$) *in vivo* was 4.83 ± 2.65 h following a single oral gavage administration of OA at a dosage of 120 mg·kg^{-1} [82]. The oral bioavailability of the prodrug in rats was 1.21% ± 0.22% when compared to intravenous administration. Although the oral bioavailability of OA is relatively low, administering high oral doses can yield an area under the curve (*AUC*) comparable to that achieved through intravenous administration. For instance, an oral dose of 50 mg·kg^{-1} in rats produces an *AUC* similar to that of an intravenous dose of 2 mg·kg^{-1} [83]. Despite OA demonstrating favorable *in vitro* membrane permeability, its intestinal absorption is restricted by efficient glucuronidation or sulfation in intestinal cells [71]. OG, which possesses a lower log *P* value and higher solubility than OA, exhibits inferior intestinal permeability. Following oral administration in rats, both OA and OG are extensively distributed throughout body tissues, with higher concentrations of OA and its metabolites detected in the intestines, stomach, liver, and plasma relative to other tissues. Most tissues reach peak concentration levels within 2 h post-administration, with concentrations beginning to decline after 6 h [83]. OA is predominantly excreted *via* feces, with an excretion rate reaching to 45.45%, likely attributable to its incomplete absorption. OG is the main metabolite present in bile and urine samples. The pharmacokinetics of OA may assist in comprehending its therapeutic implications in the liver. Understanding the pharmacokinetics of OA may provide insights into its therapeutic implications for liver conditions. Due to enterohepatic circulation, OA is particularly concentrated in the liver, thereby enhancing its efficacy in treating hepatic disorders. Consequently, OA is integral to the management of liver diseases, indicating that its mechanism of action may also involve the modulation of metabolites associated with liver-related pathologies.

Furthermore, orally administered OA has been demonstrated to be safe and well-tolerated, exhibiting a broad safety window and no indications of hepatotoxicity or nephrotoxicity. Several studies showed that OA ranging from 30–300 mg·kg^{-1} administered orally significantly inhibited tumor growth in multiple xenograft models without affecting body weight, peripheral blood cells and vital organs, such as heart, kidney, liver, and spleen [84-86]. More recently, Wei et al. demonstrated that 50 mg·kg^{-1} of OA effectively counteracted TMZ-induced weight loss, leukocyte count reduction, and lung injury, indicating the safety of OA in normal cells or organs [27]. In reproductive toxicity studies involving oral administration, the No Observed Adverse Effect Level (NOAEL) was identified as 2400 mg·kg^{-1} for mice or 810 mg·kg^{-1} for Beagle dogs. This indicates that the NOAEL for experimental animals is at least eight times greater than the effective high dose of 300 mg·kg^{-1} for mice.

5. Polypharmacology of OA against hepatic disorders

OA demonstrates significant therapeutic potential across various liver diseases, including the mitigation of liver injury, reduction of liver fibrosis, suppression of non-alcoholic fatty liver disease (NAFLD)/non-alcoholic steatohepatitis (NASH), regulation of autoimmune hepatitis (AIH) (Fig. 3), and inhibition of HCC. These effects are observed at dosages ranging from 20–300 mg·kg^{-1} *in vivo* and 50–100 μmol·L^{-1} *in vitro* (Fig. 4, Table S2). Elucidating the mechanisms underlying OA's therapeutic effects is crucial for advancing our understanding of its potential applications.

5.1. Liver fibrosis

It is estimated that more than 80% of HCC cases originate from liver fibrosis or cirrhosis. Liver fibrosis is characterized by an abnormal wound healing response, primarily manifested through excessive accumulation of extracellular matrix (ECM) proteins and the loss of normal liver tissue architecture. The development of liver fibrosis can be attributed to various factors, including chronic viral hepatitis, alcohol consumption, drug-induced liver injury, and genetic diseases, metabolic disorders, and autoimmune diseases [87, 88]. Despite the absence of FDA-approved anti-fibrotic drugs for liver fibrosis, the most effective strategy for its prevention and treatment remains the elimination of causative factors, thereby leveraging the liver's intrinsic self-repair mechanisms [89]. However, this recovery process is relatively slow, and, with the exception of viral hepatitis, the complete eradication of causative factors is often unfeasible, complicating efforts to prevent the progression of liver fibrosis and the severe complications that may threaten life. Consequently, there is a pressing need to investigate novel therapeutic strategies or pharmacological agents aimed at halting the advancement of liver fibrosis and potentially reversing the condition. The pathophysiology of liver fibrosis is complex, involving multiple cell types and signaling pathways, with hepatic stellate cells (HSCs) playing a pivotal role in this process [90, 91]. In a healthy liver, HSCs are in a quiescent state, primarily responsible for fat storage, vitamin A metabolism, and the secretion of ECM proteins to maintain ECM homeostasis [92, 93]. Upon sustained liver injury, damaged cells release pro-inflammatory or pro-fibrotic factors that activate relevant signaling pathways, leading to the activation of HSCs. Targeting HSCs to inhibit their activation or induce their apoptosis can reverse liver fibrosis, thereby promoting the regression of the condition [94-97].

A substantial body of evidence suggests that OA can attenuate pathological alterations in mice with liver fibrosis induced by carbon tetrachloride (CCl_4), leading to a reduction in collagen deposition and a significant inhibition of liver fibrosis progression. Research has shown that OA induces apoptosis in HSCs through the activation of the endoplasmic reticulum stress (ERS) pathway [98]. Additionally, OA has been found to inhibit the secretion of pro-inflammatory cytokines from activated HSCs by clearing reactive oxygen species (ROS) and suppressing the phosphatidylinositol 3-kinase (PI3K)/protein kinase B (Akt)/mammalian target of rapamycin (mTOR) pathway, thereby promoting autophagy and diminishing HSC activation [99-101]. The liver possesses a robust regenerative capacity, wherein cellular senescence and regeneration play critical roles in hepatic disorders [102]. OA induces the senescence of activated HSCs *via* the activation of the cyclic guanosine monophosphate-adenosine monophosphate synthase (cGAS)-stimulator ofinterferon genes (STING) pathway. This process involves the down-regulation of DNMT3A expression, influ-

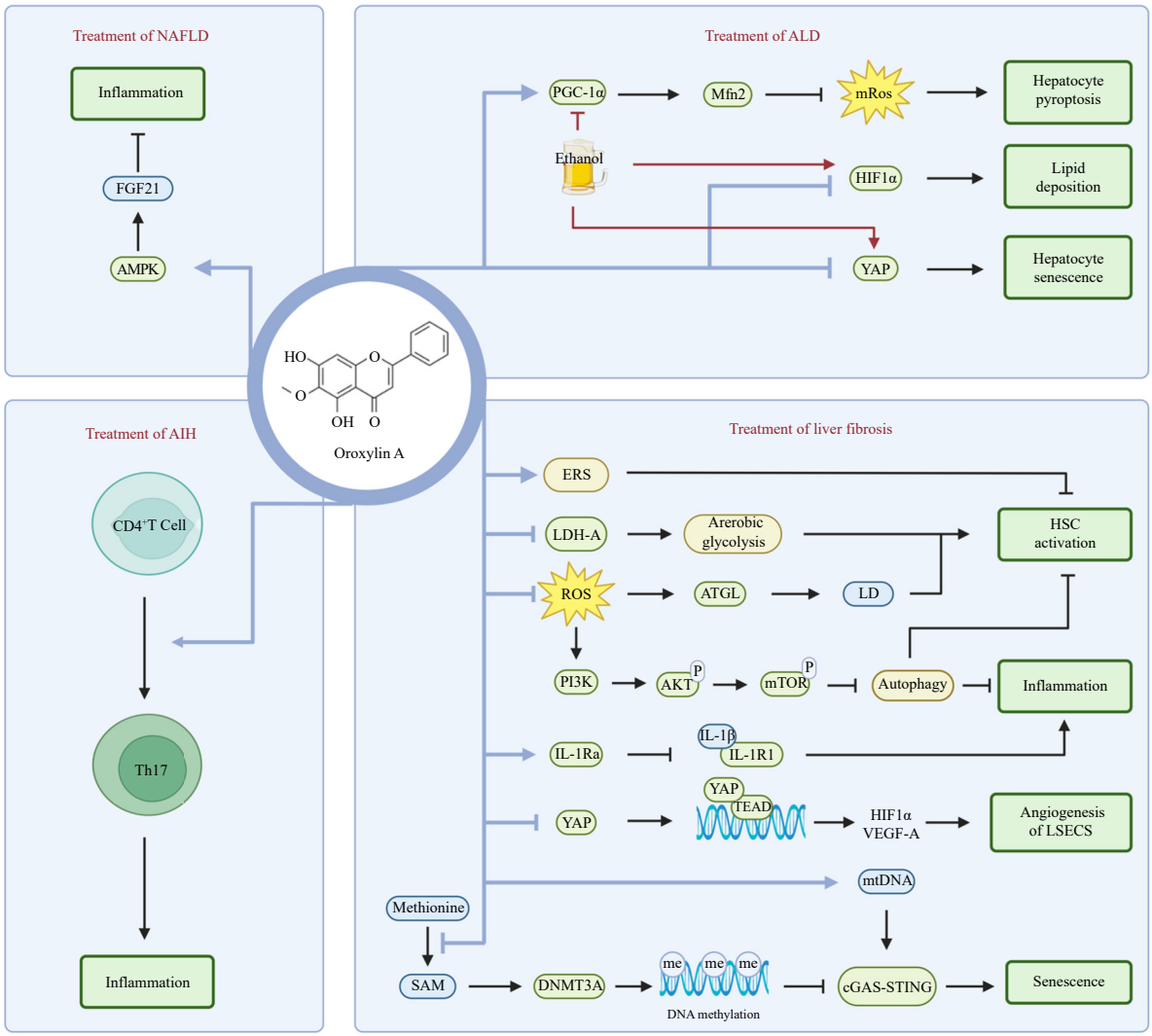

Fig. 3 Molecular mechanisms of OA on chronic liver diseases, including liver fibrosis, alcoholic liver disease (ALD), non-alcoholic fatty liver disease (NAFLD), and autoimmune hepatitis (AIH). OA alleviates of fatty liver disease and hepatitis by the regulation lipid deposition, the suppression of stellate cell activation, the protection of hepatocytes, the inhibition of angiogenesis and the modulation of Treg/Th17 balance. "↓", promotion; "⊥", inhibition. Created with BioRender.com.

enced by the levels of *S*-adenosylmethionine (SAM), a methionine cycling metabolite in the cell, which leads to hypomethylation of the *cGAS* gene and subsequent activation of the cGAS-STING pathway. The activation of this pathway promotes the secretion of cytokines such as interferon-β (IFN-β), which in turn regulates HSC ferritinophagy, induces oxidative damage, and ultimately contributes to HSC senescence [103, 104]. The depletion of lipid droplets containing retinoic acid is critical to HSC activation. Research has demonstrated that OA reverses the decrease in lipid droplet content and HSC activation by modulating ROS levels and reducing the expression of adipose triglyceride lipase (ATGL), an enzyme involved in lipolysis [105]. Furthermore, OA inhibits angiogenesis of LSECs in liver fibrosis through suppression of yes associated protein (YAP)/hypoxia-inducible factor 1α (HIF-1α) signaling [106].

5.2. Fatty liver disease

NAFLD and alcoholic liver disease (ALD) are the primary causes of chronic liver disease globally. In many patients, both metabolic dysfunction and alcohol consumption coexist as etiological factors of hepatic steatosis [107]. A significant majority, exceeding 80%, of individuals diagnosed with NAFLD are categorized as having NAFL, while less than 20% progress to NASH [108]. Patients diagnosed with NASH are at risk of fibrosis progression, cirrhosis, liver decompensation, and HCC over time [109]. On March 14, 2024, Rezdiffra received approval for marketing in the United States as the first new drug specifically targeting NASH patients with liver fibrosis. Currently, an increasing number of studies are focusing on natural compounds derived from medicinal plants, which have emerged as a promising avenue for the treatment of NASH [109-111]. The therapeutic potential of OA in managing NAFLD is gaining increasing recognition. OA treatment decreased the expression of phospho-NFκB and the secretion of tumor necrosis factor α (TNF-α) and monocyte chemoattractant protein-1 (MCP-1) in hepatocytes. Fibroblast growth factor 21 (FGF21) has recently been identified as a promising drug candidate for metabolic diseases [112, 113]. OA has been found to mitigate inflammation *via* the AMPK/FGF21 pathway, thereby reducing lipid accumulation, the expression of lipogenesis-related proteins, and apoptosis in palmitate-treated primary mouse hepatocytes [30].

The pathogenesis of ALD involves multiple mechanisms, including dysregulated lipid metabolism and accumulation, immune-inflammatory responses, oxidative stress, and mitochondrial dysfunction [114]. A study demonstrated that in a model of ethanol-induced lipid droplet accumulation in human liver L02 cell lines, OA significantly reduced the accumulation of lipid droplets. This effect was attributed to the inhibition of ethanol-induced nuclear translocation of HIF-1α [115]. Furthermore, a subsequent study demonstrated that OA inhibited ethanol-induced hepato-

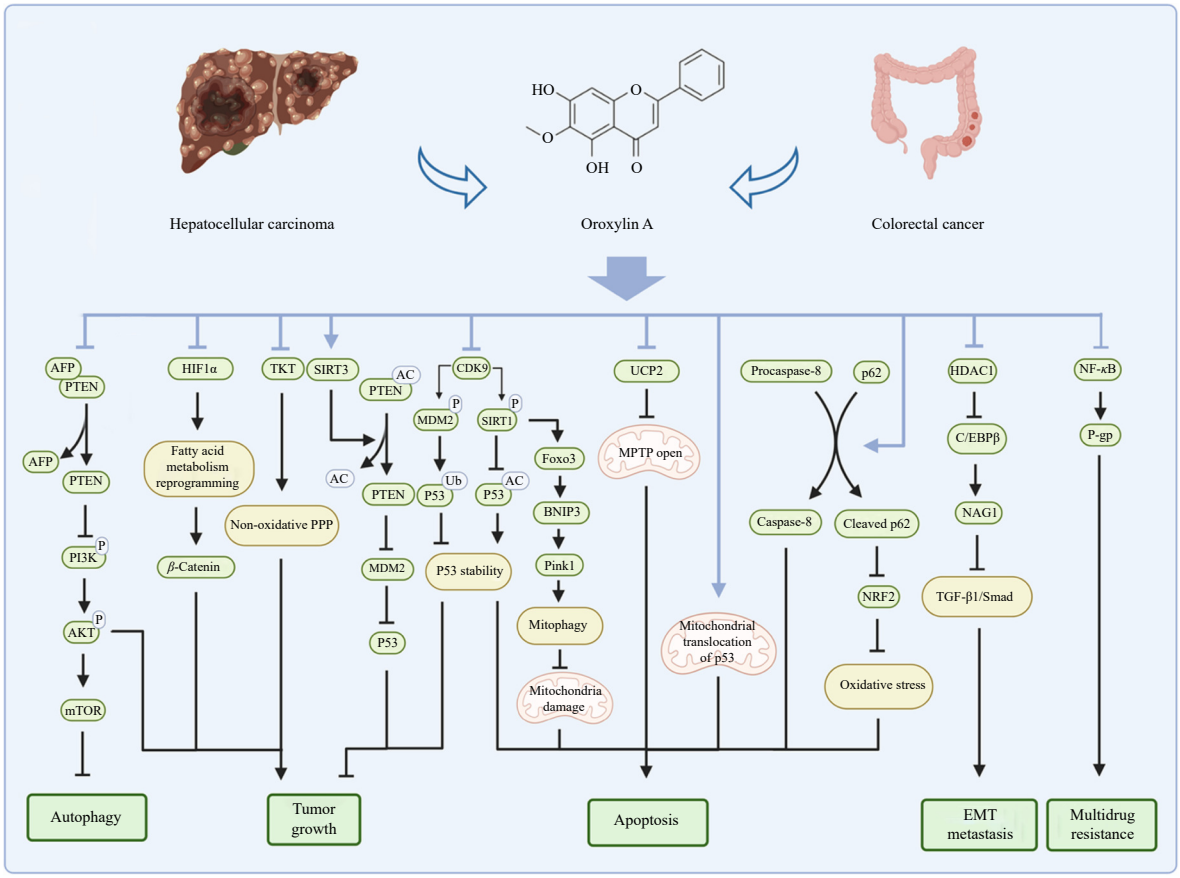

Fig. 4 Molecular mechanisms of OA the treatment of hepatocellular carcinoma and colorectal cancer. OA demonstrates its antitumor properties through various mechanisms, which encompass the inhibition of tumor proliferation, the facilitation of apoptosis, the suppression of EMT and metastatic processes, the mitigation of multidrug resistance, and the induction of autophagy. "↓", promotion; "⊥", inhibition. Created with BioRender.com.

cyte senescence and mitigated alcoholic liver injury by activating YAP [116]. Moreover, OA significantly reduced the severity of ALD in mice subjected to Lieber-DeCarli diet by suppressing hepatocyte pyroptosis. This protective effect was mediated through the reduction of ROS accumulation *via* the PGC-1α/Mfn2 pathway signaling, and inhibiting hepatocyte pyroptosis through the NOD-like receptor protein 3 (NLRP3) inflammasome-dependent canonical caspase-1 pathway [117].

5.3. Hepatitis & liver injury

Chronic liver diseases are characterized by inflammatory responses and dysregulation of immune mechanisms within the liver [118]. AIH is an immune-mediated inflammatory liver disease with a prevalence of 17.44 per 100 000 individuals, predominantly affecting females [119]. The onset of AIH is attributed to a combination of specific genetic predispositions and environmental factors, leading to impaired immune regulation and a T-lymphocyte-mediated immune response against hepatocyte autoantigens [120]. OA has demonstrated efficacy in mitigating AIH in a concanavalin A (Con A)-induced murine model. This therapeutic effect is associated with OA's capacity to suppress inflammatory responses and modulate the balance between regulatory T cells (Tregs) and T helper (Th17) cells, thereby promoting a shift towards anti-inflammatory Tregs [121]. The Th17/Treg imbalance mediates hepatic intolerance to exogenous lipopolysaccharide (LPS) and exacerbates liver injury through excessive immune response [122].

Acute liver injury (ALI) is characterized by extensive hepatocyte necrosis, leading to rapid deterioration of liver function and, in some cases, acute liver failure. The primary etiologies of ALI include paracetamol toxicity, drug-induced liver injury, ischemia, viral infections, and AIH [123]. While liver transplantation remains the definitive treatment for acute liver failure, certain natural products, such as berberine, are being investigated as potential therapeutic agents [124, 125]. OA has demonstrated hepatoprotective properties across various models of liver injury. OA significantly promotes liver structural remodeling and functional recovery through the interleukin (IL)-1Ra/IL-1RI signaling pathway, effectively mitigating CCl_4-induced liver injury in mice. Furthermore, OA was found to initiate liver regeneration during the acute phase and promptly terminate regeneration upon functional recovery [126]. Another study revealed that OA conferred protection against LPS and/or galactosamine (GalN)-induced liver injury by activating the Nrf2 pathway and inhibiting the TLR4 signaling pathway [127].

5.4. HCC

According to recent incidence statistics of malignant tumors in China, CRC (517 100 cases) and liver cancer (367 700 cases) rank as the second and fourth most prevalent cancers, respectively. Moreover, digestive system cancers exhibit high mortality rates, with liver cancer (316 500 deaths), stomach cancer (260 400 deaths), CRC (240 000 deaths), and esophageal cancer (187 500 deaths) ranking second to fourth in cancer-related mortality [128]. Notably, cancers of the digestive system often present with subtle early symptoms, frequently resulting in diagnosis at advanced stages where the effectiveness of surgical intervention, radiotherapy, and chemotherapy is significantly reduced [129, 130].

HCC is a highly prevalent and aggressive malignant tumor, with risk factors including chronic hepatitis B and C, alcohol addiction, metabolic liver diseases, and exposure to dietary toxins such as aflatoxins and aristolochic acid [131]. Recent studies have

emphasized the significant therapeutic potential of OA in HCC treatment. Research demonstrates that OA induces apoptosis in liver cancer cells through various mechanisms, including the downregulation of murine double minute 2 (MDM2) expression and the stabilization of p53 [132], activation of caspase-8 and degradation of p62/SQSTM1 [133], as well as the induction of mitochondrial apoptosis *via* modulation of the mitochondrial apoptosis-induced channel (MAC) [134], and the inhibition of TFAM-mediated mitophagy [135]. Furthermore, OA promotes Beclin 1-mediated autophagy in liver cancer cells by inhibiting the PI3K-phosphatase and tensin homolog (PTEN)-Akt-mTOR signaling pathway [136]. An additional investigation revealed that OA activated hydrogen peroxide (H_2O_2)-mediated unfolded protein response (UPR), resulting in the aberrant activation of the PERK-eIF2α-ATF4-CHOP pathway and subsequent activation of TRB3. This leads to the inhibition of the Akt signaling pathway and preferential suppression of liver cancer cells over normal hepatocytes [137]. Metabolic reprogramming is a crucial factor in the initiation and progression of HCC [138]. OA has been shown to inhibit the expression and stability of HIF-1α under hypoxic conditions, significantly reducing lactate production and glucose uptake in HepG2 cells [139, 140]. Furthermore, additional studies have demonstrated that OA and OG modulate glycolipid metabolism switch and oxidative phosphorylation by acting as dual agonists of peroxisome proliferator-activated receptor γ (PPARγ) and PPARα, thereby reversing the metabolic reprogramming of tumor cells and inhibiting HCC proliferation [141, 142]. Another study suggests that OA is a novel transketolase inhibitor and suppresses the non-oxidative pentose phosphate pathway of HCC [143]. Moreover, OA facilitates metabolic shifts between tumor cells and immune cells, thereby enhancing the inhibition of tumor progression and improving the efficacy of immunotherapy in HCC models [85].

Targeting cyclin-dependent kinase 9 (CDK9) is regarded as a promising strategy for antitumor drug development [144]. Multiple studies have identified OA as a CDK9 inhibitor. OA demonstrates the ability to stabilize wild-type p53 (wt-p53) by inhibiting the CDK9-mediated activation of SIRT1 and mouse double MDM2. The restoration of wt-p53 function promotes apoptosis, impedes DNA repair, disrupts metabolism, and inhibits the progression of HCC [145]. Furthermore, OA's inhibition of CDK9 blocks PINK1-PRKN-mediated mitophagy through inactivation of the SIRT1-FOXO3-BNIP3 signaling axis, leading to mitochondrial dysfunction. This dysfunction reduces drug resistance in tumor cells, thereby significantly enhancing the therapeutic efficacy of sorafenib and doxorubicin [146]. The efficacy of HCC treatment is often limited by drug resistance [147]. Several studies have indicated that OA possesses the ability to overcome resistance. OA has been observed to enhance 5-fluorouracil (5-FU)-induced apoptosis in HepG2 cells by increasing the expressions of p53 and cleaved PARP while decreasing the expression of anti-apoptotic proteins such as cyclooxygenase-2 (COX-2) and Bcl-2 [148]. Additionally, OA significantly reverses drug resistance in 5-FU-resistant BEL7402 cell lines and decreases P-glycoprotein expression by inhibiting the nuclear factor κB (NF-κB) signaling pathway [149]. Cell adhesion-mediated drug resistance (CAM-DR) limits the efficacy of cancer treatment [150], with integrins emerging as attractive targets for cancer therapeutics [151]. OA reverses CAM-DR by inhibiting integrin and its associated pathways, thereby enhancing the efficacy of paclitaxel [152]. The high invasiveness of HCC directly contributes to its lethality. OA has been demonstrated to inhibit transforming growth factor β1 (TGF-β1)-induced EMT and metastasis of HCC by upregulating the expression of non-steroidal anti-inflammatory drug-activated gene-1 (NAG-1) and obstructing TGF-β1/Smad signaling [153, 154]. Another study indicates that OA inhibits HCC growth by disrupting the interaction between AFP and PTEN, and reducing lung metastasis of HCC *via* angiogenesis inhibition [155].

6. Pharmacologic actions of OA against GI disorders

The UGT metabolite resulting from oral OA administration tends to accumulate in the intestinal tissue at elevated concentrations for extended periods, facilitating enterohepatic circulation. This accumulation plays a crucial role in the treatment of intestinal disorders (Fig. 4, Table S3).

6.1. CRC

The rising incidence of CRC can be attributed to multiple factors, including an aging population, poor dietary habits, and an increase in risk factors such as smoking, sedentary behavior, and obesity [156]. Lipid metabolism plays a crucial role in maintaining the energy balance of CRC cells [157]. Recent studies have demonstrated that OA can deactivate HIF-1α and alter the fatty acid metabolism of human CRC HCT116 cells. The rapid decrease in fatty acid levels induced by OA inhibits the nuclear translocation of *β*-catenin and disrupts the Wnt signaling pathway, leading to G_2/M cell cycle arrest and growth inhibition under hypoxic conditions [158]. Another study revealed that OA prevented CRC development by inhibiting aerobic glycolysis while promoting mitochondrial respiration. This effect is mediated through the enhancement of SIRT3-mediated deacetylation, which prevents p53 degradation by MDM2 and inhibits glycolysis in cancer cells with wt-p53 [159]. Moreover, OA induces apoptosis in human CRC CaCo-2 cells by inhibiting UCP2 and facilitating the mitochondrial translocation of p53, resulting in ROS-mediated MPTP opening and mitochondrial apoptosis [160, 161]. Although 5-FU remains the primary agent in first-line chemotherapy regimens for CRC, resistance to this drug is common [162, 163]. Notably, OA has been shown to enhance the sensitivity of CRC HT-29 cells to 5-FU both *in vitro* and *in vivo* by inhibiting COX-2 expression [164].

Additionally, chronic colitis has been associated with an elevated risk of CRC development [156, 165]. Research indicates that OA can inhibit colitis-associated carcinogenesis by modulating the IL-6/STAT3 signaling pathway in an azoxymethane/dextran sodium sulfate (AOM/DSS) mouse model and in HCT116 cells [166]. Furthermore, OA inhibited the proliferation of HCT116 cells stimulated by LPS-activated THP-1 cells by regulating the NF-κB signaling pathway [167].

6.2. Inflammatory bowel disease (IBD)

IBD primarily comprises two conditions: Crohn's disease (CD) and ulcerative colitis (UC), both characterized by chronic inflammation of the GI tract and affecting 0.3%–0.5% of the global population [168]. IBD is distinguished by alternating phases of clinical relapse and remission, with symptoms primarily manifesting as diarrhea, abdominal pain, and rectal bleeding [169]. The pathogenesis of IBD is thought to result from a multifactorial interaction involving genetic susceptibility, gut microbiota composition, dysregulated immune responses, and a compromised intestinal mucosal barrier [170]. Despite significant advancements in the therapeutic management of IBD through chemical agents and biological therapies, such as aminosalicylates, corticosteroids, antibiotics, and anti-TNF agents, complete healing remains elusive, and side effects are inevitable. Consequently, numerous studies have identified natural products as promising therapeutic alternatives for IBD, acting through various mechanisms including anti-inflammatory, anti-oxidant, anti-fibrotic, and anti-apoptotic effects [171-173].

Several natural products and TCM have been proposed to mitigate metabolic syndrome by improving abnormal metabolism and modulating gut microbiota [174-177]. OA has been shown to alleviate low-grade colonic inflammation induced by dietary fiber deficiency in murine models, thereby mitigating colitis [178]. Addi-

tional research has demonstrated that OA can diminish inflammatory cell infiltration and DSS-induced colonic tissue damage by decreasing myeloperoxidase (MPO) and inducible nitric oxide synthase (iNOS) activity [179]. Furthermore, OA has been observed to inhibit the activation of the NLRP3 inflammasome by obstructing the NF-κB pathway and restraining inflammasome assembly, which subsequently leads to reduced levels of caspase-1, IL-1β, and NLRP3 in colonic samples from DSS-induced colitis mice, thereby ameliorating intestinal inflammation [180].

7. Possible connections of OA and natural flavonoid to gut-liver axis

7.1. Liver-gut connections

The liver and GI tract are integral to the maintenance of homeostasis and exhibit closely interrelated functions, engaging in bidirectional communication through various signaling pathways that collectively form the gut-liver axis. As the largest and most central digestive organ in the body, the liver functions not only as a critical barrier to limit bacterial dissemination but also as the primary site for extensive metabolite processing [181]. The liver regulates the structure and function of the intestinal flora through the secretion of bile acids and other metabolites, thereby maintaining a balance within the intestinal flora [182]. Intestinal bacteria are essential for the enterohepatic circulation of bile acids, facilitating the reabsorption of approximately 95% of bile acids by the intestinal wall, which compensates for the loss of hepatocytes [183].

Any dysfunction in the liver, GI tract, or gut microbiota can trigger an inflammatory response [184]. Hepatic disorders are often characterized by changes in the levels of inflammatory cytokines, such as IFN-γ, TGF-β1, IL-6, IL-4, IL-7, IL-11, and IL-33 [185-188]. Recent studies suggest that alterations in the gut microbiota may represent a promising target for the prevention and management of liver diseases [189-191]. In the context of obesity, the gut microbiota may independently contribute to the pathogenesis of NAFLD, as evidenced by distinctive alterations at the phylum, genus, and species levels that affect the host's response to a high-fat diet [192]. The gut flora metabolizes intestinal contents into various compounds, including fatty acids, vitamins, amino acids, and bile salts. Notably, the intestinal bacterial metabolite deoxycholic acid in obese mice has been shown to promote the development of HCC by inducing a senescence-associated secretory phenotype (SASP) in HSCs [193]. Furthermore, gut microbes interact with the host and influence various target organs, playing a significant role in the crosstalk of the gut-liver axis, contributing to the inhibition of oxidative stress, the suppression of inflammation, and the prevention of hepatic lipid deposition [194].

7.2. Possible effects and potential relevance of OA on the gut-liver axis

The paradoxical relationship between the limited bioavailability of orally administrated natural flavonoids and their extensive biological activity presents an intriguing phenomenon [9, 195]. Some studies suggest that the health benefits of natural flavonoids may rely on their positive modulation of the microbiome-gut-liver axis rather than solely on their poor bioavailability. Currently, there is limited research focused on the impact of OA on intestinal microbiota. Lu's team has demonstrated that OA preserves the colonic mucus barrier, thereby reducing susceptibility to disease by restoring a dietary fiber-deprived gut microbiota [178]. Notably, OA significantly increased the levels of *Eubacterium coprostanoligenes*, which in turn conferred protection against colitis and carcinogenesis in murine models. Furthermore, the metabolite of OA, OG, has been shown to influence the composition of the intestinal microbiota and the production of short-chain fatty acids (SCFAs) within the gut [196]. The enterohepatic circulation facilitates the attainment of elevated local concentrations of OA and its metabolites in the liver and intestine, thereby sustaining these concentrations over extended periods and continuously modulating various signaling pathways [83].

The liver and gut are interconnected primarily through the physiological structures of the portal vein and biliary system. The reported therapeutic targets of OA for the treatment of hepatic and GI diseases, including PPARγ/α [142] and SIRT1 [146], are implicated in the gut-liver axis and are involved in the regulation of metabolism and inflammatory responses. The farnesoid X receptor (FXR), which is abundantly expressed in both liver and intestines, serves as a natural receptor for bile acids and may regulate the expression of pro-inflammatory cytokines such as TNF-α, NF-κB and/or TGF-β1 through various signaling pathways across a range of diseases [197]. SIRT1 has been shown to influence FXR activity [198], suggesting that OA may modulate bile acid metabolism and alleviate bile acid burden in hepatocytes by inhibiting SIRT1, thereby inactivating FXR. Nevertheless, there is still a lack of experimental evidence to confirm whether OA activates or antagonizes FXR. Additionally, both OA and its glucoside OG function as dual agonists of PPARγ/α, which are crucial in regulating cytochrome P450 (CYP) and UGT enzymes, both of which play vital roles in bile acid metabolism and glucuronidation, respectively [199, 200]. Consequently, it is plausible that OA may engage with the intestinal microbiota and facilitate bidirectional communication within the gut-liver axis through bile acid metabolism or FXR signaling, thereby contributing to its diverse pharmacological effects (Fig. 5).

7.3. Effects of other natural flavonoid on the gut-liver axis

In addition to OA, several other natural flavonoids, including baicalin, baicalein, and curcumin, have been identified as modulators of the microbiome-gut-liver axis. Multiple studies suggest that baicalin, a structural analogue of OA, may be involved in hepatic and intestinal disorders through its regulation of bile acids, which play crucial roles in antibacterial activity and the remodeling of the intestinal flora. Baicalin has been shown to offer protective effects against cholestasis by reducing bile acid excretion and enhancing the activity of liver enzymes involved in bile acid metabolism [82, 201]. Furthermore, baicalin may possess therapeutic potential in addressing liver and intestinal disorders by modulating the communication between the liver and intestines through FXR and TGR5 pathways, which are associated with bile acids and intestinal flora [202]. The glycoside form of baicalin, baicalein, has shown efficacy in alleviating NAFLD in murine models by decreasing intestinal permeability and ameliorating intestinal barrier dysfunction [203]. Curcumin, a lipophilic polyphenol derived from turmeric, has also demonstrated significant implications for the liver-gut system [204]. Research indicates that curcumin and its metabolites can influence the microbiota composition and exhibit anti-fibrotic effects in the liver [205], while also providing hepatoprotective benefits by modulating dysbiosis of the gut microbiota and subsequently reducing the inflammatory response in the liver triggered by serum LPS [206]. Additionally, (−)-epicatechin, one of the most prevalent plant polyphenols in the human diet, has been found to ameliorate type 2 diabetes mellitus by reshaping gut microbiota structure, including the inhibition of LPS-producing bacteria and the reduction of serum LPS [207]. Moreover, various structural flavonoids derived from fruit extracts demonstrate hepatoprotective properties against alcohol-induced liver injury *via* the gut microbiota-liver axis [208].

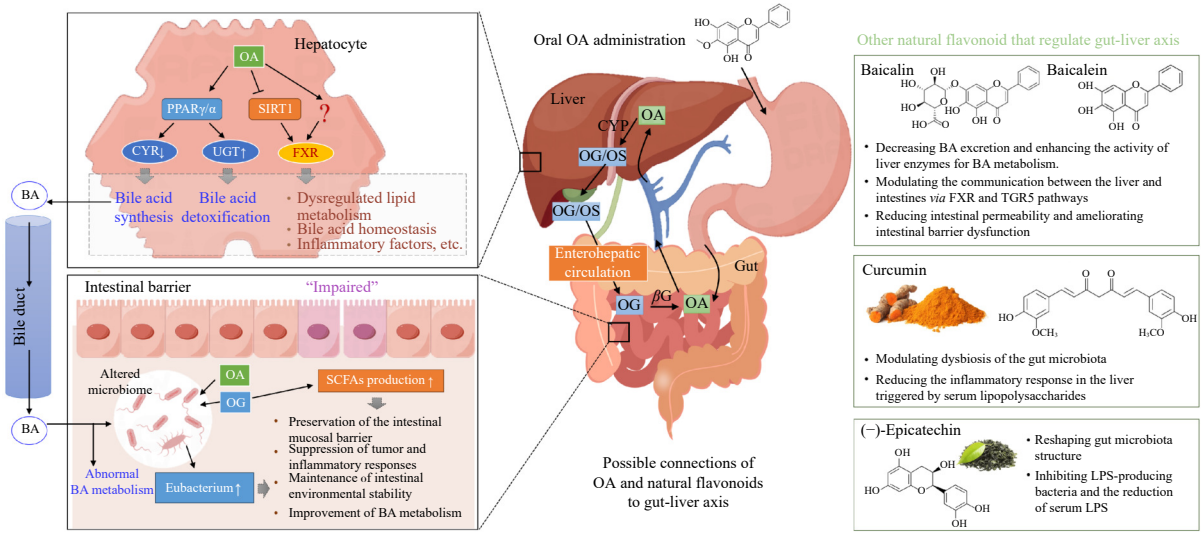

Fig. 5 Possible connections of OA and natural flavonoid to gut-liver axis. The health benefits associated with natural flavonoids, such as OA, may be attributed to their favorable modulation of the microbiome-gut-liver axis. Upon oral administration, OA is transported to the liver *via* the portal vein originating from the small intestine, where it undergoes metabolic conversion by CYP into OG and OS. Subsequently, OG is secreted into the small intestine through bile, where it is re-hydrolyzed back into OA by *β*G and subsequently transported back to the liver, establishing an enterohepatic circulation. OA may interact with the intestinal microbiota, facilitating bidirectional communication within the gut-liver axis through mechanisms such as bile acid metabolism or FXR signaling, thereby contributing to its diverse pharmacological effects in conditions such as NASH, HCC, IBD, and CRC. Specifically, OA may enhance the expression of UGT and downregulate CYP expression *via* the activation of PPARγ/α, which in turn inhibits bile acid synthesis and promotes bile acid detoxification. The activation of FXR by bile acids results in reduced hepatic lipid production and inflammation. Interestingly, OA may modulate FXR activity by inhibiting SIRT1; however, the existence of additional regulatory pathways for FXR remains to be elucidated. Following the reabsorption of bile acids in the intestine, the microbiota within a pathological intestinal environment may disrupt bile acid metabolism, exacerbating the condition. Notably, OA has been shown to increase the levels of *Eubacterium*, while OG promotes the production of SCFAs. These effects contribute to the preservation of the intestinal mucosal barrier, suppression of tumorigenic and inflammatory responses, maintenance of intestinal environmental stability, and enhancement of bile acid metabolism. In addition to OA, some other natural flavonoid, including baicalin, baicalein, curcumin, and (−)-epicatechin are reported modulate the gut-liver axis. The information contained within the gray dashed box is entirely speculative. OA: oroxylin A; OG: oroxylin A 7-*O*-glucuronide; OS: oroxylin A sodium sulfonate; CYP: cytochrome P450; *β*G: intestinal bacterial *β*-glucuronidase; BA: bile acid; UGT: 5'-diphospho-glucuronosyltransferase, FXR: farnesoid X receptor; SCFAs: short-chain fatty acids.

8. Drug delivery for OA

The efficiency and clinical applications of flavonoids, including icaritin, apigenin, berberine, quercetin and OA, have been constrained by their low content, poor bioavailability, and suboptimal *in vivo* delivery efficiency [209-211]. Recent advancements in enzyme engineering and nanotechnology have been developed to enhance the productivity and activity of these compounds, improve their delivery efficiency, and augment their therapeutic effects [212, 213]. Nanotechnology has emerged as a particularly promising approach for enhancing drug efficacy and minimizing toxicity by improving drug solubility, modifying biodistribution, and controlling release profiles [214, 215]. Researchers have proposed innovative delivery strategies for OA, including smart nanoparticles, nanostructured lipid carriers, and microsome-hydrogel systems [216-218]. The solubility of OA is substantially improved when administered in combination with other molecules in complex form. However, oral drug delivery systems for OA remain relatively unexplored.

9. Clinical trial progression of OA tablets

A phase I clinical trial was conducted to evaluate the safety, tolerability, and pharmacokinetic characteristics of OA in healthy adult volunteers in China, following both single and multiple doses, as well as the effect of food on OA after oral administration. The oral administration of 2400 mg of OA demonstrated favorable tolerability. No dose-limiting toxicities (DLT), fatalities, or serious adverse events (SAE) were reported. All observed AE were classified as mild or moderate, with no treatment discontinuations due to adverse events. The incidence of GI AEs was slightly higher following multiple doses compared to a single dose. The circulating metabolite profile aligned with findings from animal studies. OA's half-life remained consistent under both single and multiple dosing regimens, supporting a once-daily dosing schedule. Although the absolute bioavailability of OA is relatively low, food intake, particularly high-fat meals, can enhance its bioavailability (Clinical data is derived from unpublished report supplied by Nanjing Qinling Pharmaceutical Technology Co., Ltd.). The safety and pharmacokinetic data from this study have been used to support ongoing phase Ib clinical trials involving HCC patients (CTR20221352).

10. Future prospects and conclusion

Hepatic and GI disorders have emerged as the leading cause of mortality globally in recent years. Flavonoids, polyphenolic secondary metabolites present in various plants and foods [210, 219], are now well recognized to play significant biological roles and exhibit a wide range of pharmacological activities [211, 212, 220, 221]. The flavonoid compound OA has demonstrated anti-inflammatory, anti-tumor, and anti-oxidative stress properties in relation to various diseases affecting both the liver and GI system, while exhibiting minimal adverse effects. Furthermore, numerous studies have indicated that OA provides protective effects on various organs, including the liver [30, 117], heart [222], nerves [223, 224], and kidney [225]. This protective capability distinguishes OA from conventional chemotherapeutic agents. It is anticipated that OA may help mitigate the limitations associated with existing antitumor therapies.

The metabolic profile of oral administration of OA is characterized by significant distribution within the liver and intestinal tract, as well as enterohepatic recirculation, thereby playing a crucial role in the treatment of liver and GI diseases. OA influences multiple pathways and targets to modulate oxidative stress, inflammation, immune response, apoptosis and metabolic processes. This multifaceted action is particularly relevant in the management of complex hepatic and GI conditions, where inflammation, immune dysregulation, and tissue damage are critical factors in disease progression. OA has the potential to impede the advancement of chronic diseases to more severe stages and may enhance the efficacy of combination therapies, thereby improv-

ing the effectiveness of other medications and delaying the onset of drug resistance. Notably, the health benefits of OA may be attributed more to their positive modulation of the gut-liver axis than to their limited bioavailability alone. OA may facilitate communication within the microbiome-gut-liver axis through immune pathways linked to bile acids, potentially contributing to its pharmacological effects.

In conclusion, OA represents a promising therapeutic candidate for the treatment of hepatic and GI diseases. Its efficacy is underpinned by a complex interplay of mechanisms and signaling pathways. However, there remains a paucity of clinical studies and investigations into combination therapies, suggesting that the pathway to the clinical application of OA is still lengthy. Further disclosure of clinical data from OA tablets is anticipated, which will facilitate the confirmation of its poly- targets and clinical biomarkers.

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Availability of supporting information

Supporting information for this work can be obtained by contacting the corresponding authors *via* E-mail.

Declaration of competing interest

These authors have no conflict of interest to declare.

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